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EXAMINER	
SCHNIZER, RICHARD A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 11/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/872,712	BACKER ET AL.	
	Examiner	Art Unit	
	Richard Schnizer, Ph. D	1635	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *11 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-3,5-11,13-17,19-25,27-33,35-41,43-45 and 58-78* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3,5-11,13-17,19-25,27-33,35-41,43-45 and 58-78* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on *01 June 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

An amendment and an information disclosure statement were received and entered on 8/11/03.

New claims 58-78 were added as requested.

Claims 1-3, 5-11, 13-17, 19-25, 27-33, 35-41, 43-45, and 58-78 are pending and are under consideration in this Office Action.

Previously claims 10, 24, and 40 were objected, but characterized as free of the art of record. After further search and consideration, these claims are bovious as discussed further below.

Applicant originally elected for examination a species of the invention comprising a carrier molecule (copolymer), a compound (nucleic acids), an adapter (wild type S-protein fragment of bovine RNase A), a targeting ligand (growth factors), and a pharmaceutically acceptable carrier (water). This species was found to be novel and non-obvious in Paper No. 8. In accordance with MPEP 803.02, the Office extended the search to a second combination of species, *i.e.* liposomes, nucleic acids, streptavidin, antibodies, and water which were found to be anticipated by or obvious in view of Bally, (1989), Tillman (1999) or Wickham (1998). Applicant subsequently amended the claims to require that the targeting ligand must be part of a recombinant fusion protein. The species of invention comprising liposomes, nucleic acids, streptavidin, antibodies, and water remains under consideration in this Office Action, and this embodiment has been found to be obvious in the context of all claims. Further species in which the carrier is a virus were also found to be anticipated or obvious as discussed below.

Rejections Withdrawn

After further consideration, the rejection in Paper No. 12 of claims 31-33, 34-41, and 43-45 under 35 USC 112, first paragraph for lack of enablement is withdrawn. The claims are not drawn to any specific method of gene therapy, and it is known in the art that, while broad claims to gene-based therapy of diseases in general are not enabled, there are instances in which nucleic acid-based therapeutics are employed successfully. The instant invention can be viewed as a variation in the delivery compositions employed in such techniques.

The objection to the specification under 35 U.S.C. 132 over the addition of the Raines reference is withdrawn in view of Applicant's deletion of the citation of the Raines reference.

The rejection of claims 1-3, 5-9, 13-17, 19-23, 27-33, 35-39, and 43-45 under 35 USC 103 as being obvious over the combination of Bally and Curiel is withdrawn because Curiel teaches the use of streptavidin binding peptides fused to an adenoviral fiber protein, rather than streptavidin binding peptides fused to a targeting antibody as stated in the rejection.

Specification

The specification stands objected to under 35 U.S.C. 132 because the amendment filed 11/26/02 introduced new matter into the disclosure. 35 U.S.C. 132 states that no amendment shall introduce new matter into the disclosure of the invention. The added material which is not supported by the original disclosure is of the statement "the human homolog of bovine ribonuclease A is also known as ribonuclease I", and all instances of "ribonuclease I". While this is a statement of fact that is supported by the prior art, and one of skill in the field of the invention might reasonably

be expected to be aware of this fact, the record does not clearly indicate that Applicant was in possession of this information at the time the invention was filed, so the material must be objected to as new matter.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8, 11, 22, 25, 38, 41, 64, 65, 74, and 75 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims recite "human ribonuclease I". The specification as filed provided no support for the term "human ribonuclease I", reciting instead "human ribonuclease A".

Response to Arguments

Applicant's arguments filed 8/11/03 have been fully considered but are not persuasive. Previously in Paper No. 11 Applicant indicated that the specification and claims, while referring to "human ribonuclease A", should actually have referred to "human ribonuclease I" because this is the art-recognized term for the human homologue of bovine RNase A. At pages 21-23 of the current response Applicant

reiterates this argument and relies for support on Raines et al (1998) and a copy of the Sigma product information sheet for bovine ribonuclease A.

The Raines document teaches that humans contain at least five distinct homologues of bovine RNase A including RNases 1-4 and angiogenin. However, Applicant has provided no evidence that the human homologue of bovine RNase A that was contemplated in the originally filed specification was RNase 1 and not one or more of RNases 2-4 or angiogenin. The Sigma product information sheet lists synonyms for bovine RNase A, including RNase I, but does not list among the synonyms "human RNase I" as currently claimed, and therefore does not support the contention that Applicant originally intended human RNase I rather than human RNase A. For these reasons the rejection is maintained.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 30 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 30 is indefinite because it is unclear what is intended by "pathophysiological conditions that depend on cells that can be detected or affected via target mediates delivery". More specifically, it is unclear what is intended by the word "depend" in passage. The metes and bounds of the claim are unclear because the

specification and claims provide no standard for determining whether or not a pathophysiological condition depends on a particular cell.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-3, 5-7, 9, 13-17, 19-21, 23, 27-29, 31-33, 35-37, 39, and 43-45 are rejected under 35 U.S.C. 102(e) as being anticipated by Curiel et al (US Patent 6,284,742, issued 9/4/01), as evidenced by Da Silva et al (Leukemia 8(5): 885-889, 1994).

Curiel teaches a delivery vehicle comprising an adenoviral vector encoding a polynucleotide for in vivo delivery. The tropism of the virus is modified through the use of a fusion protein consisting of two single chain antibodies, one of which recognizes the adenovirus knob domain of the fiber protein, and one of which is directed to a cell surface antigen, e.g. CD40. See claim 1 at columns 18 and 19; paragraph bridging columns 9 and 10, column 10, lines 13-15. The knob domain of adenoviral fiber protein is considered to be an adapter that is covalently attached to fiber protein. The fiber

protein is a polymer as required by e.g. claim 5. The portion of the fusion protein separating the recognition domains is considered to be a spacer, as required by e.g. claim 14. The composition may be delivered in water as required by e.g. claim 29.

Claims 13, 27, and 43 are included in this rejection because they require that the target of the targeting fusion protein is a receptor found on a cell expressing a receptor for vascular endothelial growth factor. Curiel teaches that B cells can be targets for the vector recited in claim 1 because B cells express CD40. Da Silva teaches that some B cells also express a VEGF receptor (FLT3), see abstract.

Thus Curiel anticipates the claims.

Claims 1-3, 5-7, 9, 14-17, 19-21, 23, and 28 are rejected under 35 U.S.C. 102(b) as being anticipated by Valerio et al (WO 97/05266, published 2/13/97).

Valerio teaches a method of producing gene delivery vehicles which can be transferred to pre-selected cell types by using targeting conjugates. The gene delivery vehicles comprise: 1) the gene of interest; 2) a viral capsid or envelope carrying a member of a specific binding pair, the counterpart of which is not directly associated with the surface of the target cell. The targeting conjugates are composed of the counterpart member of the specific binding pair linked to a targeting moiety which is a cell-type specific ligand. See abstract. The first member of the binding pair may be covalently attached to the carrier e.g. as a fusion to a capsid protein. See paragraph bridging columns 8 and 9. The targeting conjugate may be a fusion protein. See page 9, lines 14-23. See also page 16, lines 8-27 which teaches how to use a leucine zipper

motif as a binding partner in a targeting fusion protein. This passage also discusses the use of spacers for separating the targeting moiety and the binding pair member. Valerio teaches that the targeting moiety may be an antibody. See page 13, lines 21-32, and page 16, lines 16-32

In terms of the instantly claimed invention, the virus of Valerio corresponds to the carrier, the first member of the specific binding pair corresponds to the adapter, the second member of the binding pair corresponds to the recognition portion of the targeting fusion protein, and the targeting moiety corresponds to the targeting portion of the targeting fusion protein.

Thus Valerio anticipates the claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claim 30 is rejected under 35 U.S.C. 103(a) as being unpatentable over Curiel et al (US Patent 6,284,742, issued 9/4/01).

Curiel teaches a delivery vehicle comprising an adenoviral vector encoding a polynucleotide for in vivo delivery. The tropism of the virus is modified through the use of a fusion protein consisting of two single chain antibodies, one of which recognizes the adenovirus knob domain of the fiber protein, and one of which is directed to a cell

surface antigen, e.g. CD40. See claim 1 at columns 18 and 19; paragraph bridging columns 9 and 10, column 10, lines 13-15. The knob domain of adenoviral fiber protein is considered to be an adapter that is covalently attached to fiber protein.

Curiel does not explicitly teach the organization of the elements of the composition into an article of manufacture with packaging material and instructions for use. However, it would have been obvious to organize the materials of Curiel into a package with instructions for use because one of skill in the art appreciates that organizing experimental reagents prior to use and following established protocols is standard laboratory practice which reduces the frequency of errors.

Thus the invention as a whole was *prima facie* obvious.

Claims 1, 8, 15, and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valerio et al (WO 97/05266, published 2/13/97), in view of Skerra et al (US Patent 5,506,121, issued 4/9/96).

Valerio teaches a method of producing gene delivery vehicles which can be transferred to pre-selected cell types by using targeting conjugates. The gene delivery vehicles comprise: 1) the gene of interest; 2) a viral capsid or envelope carrying a member of a specific binding pair, the counterpart of which is not directly associated with the surface of the target cell. The targeting conjugates are composed of the counterpart member of the specific binding pair linked to a targeting moiety which is a cell-type specific ligand. The member of the specific binding pair present on the viral vehicles can be, for example, streptavidin. See abstract and column 8, lines 15-35.

The targeting conjugate may be a fusion protein. See page 9, lines 14-23. See also page 16, lines 8-27. This passage also discusses the use of spacers for separating the targeting moiety and the binding pair member. Valerio teaches that the targeting moiety may be an antibody. See page 13, lines 21-32, and page 16, lines 16-32

Valerio does not teach a targeting fusion protein that provides a binding partner for streptavidin.

Skerra teaches methods and constructs for making fusions to peptides with binding affinity for streptavidin. See abstract.

It would have been obvious to one of ordinary skill in the art to use the fusion constructs of in making a fusion targeting protein as taught by Valerio, e.g. a streptavidin binding peptide/targeting antibody fusion. One would have been motivated to do so because Valerio explicitly teaches that streptavidin may be used as a binding partner attached to a carrier vehicle, that targeting conjugates comprising a binding partner for streptavidin may be used, that targeting moieties may be antibodies, and that targeting conjugates may be fusion proteins. Further, the fusion protein of Skerra can be produced in large quantities by recombinant methods, and easily purified on a streptavidin affinity column. In contrast, other recombinantly produced targeting ligands would have to be biotinylated prior to use in the system of Valerio, thereby requiring further preparation steps, more time, and possible loss of material.

Thus the invention as a whole was *prima facie* obvious.

Claims 1, 10, 13, 15, 24, 27, 58-63, 66-73, and 76-77 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valerio et al (WO 97/05266, published 2/13/97), in view of Allen et al (US 2001/038851, published 11/8/01), and Tischer et al (US 5,194,596, issued 3/16/93).

The teachings of Valerio are summarized above.

Valerio does not teach the use of VEGF 121 as a targeting moiety.

Allen teaches that VEGF can be used as a targeting moiety in delivery complexes.

Tischer teaches that VEGF 121 is an art recognized equivalent of VEGF in terms of its function in wound healing. See column 3, line 67 to column 4, line 9, Fig, 7, and column 10, lines 63-68. Clearly this function entails binding its receptor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use VEGF 121 as a targeting moiety in a fusion targeting construct of Valerio. One would have been motivated to do so because Valerio teaches that ligands that recognize cellular receptors should be used as targeting moieties, and because Allen teaches that VEGF is a useful targeting ligand in the context of delivery vehicles. It would have been obvious to use VEGF 121 as a targeting ligand because it is an art recognized variant of VEGF. See Tischer above. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ

532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case the essential function and intended use of VEGF/VEGF 121 is to recognize and bind to the receptor.

Thus the invention as a whole was *prima facie* obvious.

Claims 1, 8, 11, 15, 22, and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valerio et al (WO 97/05266, published 2/13/97), in view of Theodore et al (US Patent 6,075,010, issued 6/13/00).

The teachings of Valerio are summarized above.

Valerio does not teach the use of S protein and S-peptide as a binding pair or, more specifically, the use of S protein as an adapter and the use of S-peptide as a recognition moiety in a targeting fusion protein.

Theodore teaches the use of bovine S-peptide and S-protein as a binding pair in bipartite targeting compositions, particularly as an equivalent of the streptavidin/biotin binding pair. Either S-peptide or S-protein may be attached to a carrier while the opposite binding partner is fused to a targeting moiety such as an antibody. See column 53, line 33 to column 56, line 31, especially column 53 lines 33-48, column 54, lines 31-36, and column 56, lines 18-31.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use S-protein and S-peptide binding pair of Theodore in the invention of

Valerio. One would have been motivated to do so because Theodore indicates that this binding pair is equivalent to other binding pairs such as the biotin streptavidin binding pair taught by Valerio.

Thus the invention as a whole was *prima facie* obvious.

Claims 58, 64, 65, 68, 74, and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valerio et al (WO 97/05266, published 2/13/97), Allen et al (US 2001/038851, published 11/8/01), and Tischer et al (US 5,194,596, issued 3/16/93), as applied to claims 1, 10, 13, 15, 24, 27, 58-63, 66-73, and 76-77 above, and further in view of Theodore et al (US Patent 6,075,010, issued 6/13/00).

The teachings of Valerio, Allen, and Tischer are summarized above and can be combined to render obvious a molecular delivery vehicle comprising a carrier covalently linked to one member of a binding pair (adapter) and a targeting conjugate comprising a targeting fusion protein comprising the other member of the binding pair fused to a VEGF 121 targeting moiety.

These references do not teach the use of S protein and S-peptide as a binding pair or, more specifically, the use of S protein as an adapter and the use of S-peptide as a recognition moiety in a targeting fusion protein.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of Valerio, Allen, and Tischer by using the S-protein and S-peptide binding pair of Theodore. One would have been motivated to do so because Theodore indicates that this binding pair is equivalent to other binding pairs such as the biotin streptavidin binding pair taught by Valerio.

Thus the invention as a whole was *prima facie* obvious.

Claims 29-37, 39, 44, and 45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valerio et al (WO 97/05266, published 2/13/97), in view of Curiel et al (US Patent 6,284,742, issued 9/4/01).

The teachings of Valerio are summarized above and render obvious a molecular delivery vehicle comprising a carrier covalently linked to one member of a binding pair (adapter) and a targeting fusion protein comprising the other member of the binding pair fused to a targeting moiety.

Valerio is silent regarding pharmaceutically acceptable carriers, and does not teach the organization of the elements of the composition into an article of manufacture with packaging material and instructions for use in vivo, or a method of delivering compounds to a target in a patient.

Curiel teaches that nucleic acid delivery vehicles may be delivered to a patient in a pharmaceutically acceptable carrier such as water. See column 10, lines 9-22. It would have been obvious to use the compositions of Valerio in the methods of Curiel because the compositions of Valerio can incorporate the same carrier (adenovirus, see e.g. page 17, lines 13-16 of Valerio), and can accommodate the same targeting moiety (antibody) and payload nucleic acid. Thus, these compositions can be viewed as equivalents in terms of function, and are sufficiently structurally similar that they should use similar pharmaceutically acceptable carriers. Further, it would have been obvious to organize the materials of Valerio into a package with instructions for use because one of skill in the art appreciates that organizing experimental reagents prior to use and

following established protocols is standard laboratory practice which reduces the frequency of errors.

Thus the invention as a whole was *prima facie* obvious.

Claims 38 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valerio et al (WO 97/05266, published 2/13/97) and Curiel et al (US Patent 6,284,742, issued 9/4/01) as applied to claims 29-37, 39, 44, and 45 above, and further in view of Theodore et al (US Patent 6,075,010, issued 6/13/00).

The teachings of Valerio and Curiel are summarized above and can be combined to render obvious methods of delivering to a patient a composition comprising a molecular delivery vehicle comprising a carrier covalently linked to one member of a binding pair (adapter) and a targeting fusion protein comprising the other member of the binding pair fused to a targeting moiety.

These references do not teach the use of S protein and S-peptide as a binding pair or, more specifically, the use of S protein as an adapter and the use of S-peptide as a recognition moiety in a targeting fusion protein.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of Valerio and Curiel by using the S-protein and S-peptide binding pair of Theodore. One would have been motivated to do so because Theodore indicates that this binding pair is equivalent to other binding pairs such as the biotin streptavidin binding pair taught by Valerio.

Thus the invention as a whole was *prima facie* obvious.

Claims 40 and 43 are rejected under 35 U.S.C. 103(a) as being unpatentable over Valerio et al (WO 97/05266, published 2/13/97) and Curiel et al (US Patent 6,284,742, issued 9/4/01) as applied to claims 29-37, 39, 44, and 45 above, and further in view of Allen et al (US 2001/038851, published 11/8/01), and Tischer et al (US 5,194,596, issued 3/16/93).

The teachings of Valerio and Curiel are summarized above and can be combined to render obvious methods of delivering to a patient a composition comprising a molecular delivery vehicle comprising a carrier covalently linked to one member of a binding pair (adapter) and a targeting fusion protein comprising the other member of the binding pair fused to a targeting moiety.

These references do not teach the use of VEGF 121 as a targeting moiety.

Allen teaches that VEGF can be used as a targeting moiety in delivery complexes.

Tischer teaches that VEGF 121 is an art recognized equivalent of VEGF in terms of its function in wound healing. See column 3, line 67 to column 4, line 9, Fig, 7, and column 10, lines 63-68. Clearly this function entails binding its receptor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use VEGF 121 as a targeting moiety in a fusion targeting construct of Valerio. One would have been motivated to do so because Valerio teaches that ligands that recognize cellular receptors should be used as targeting moieties, and because Allen teaches that VEGF is a useful targeting ligand in the context of delivery vehicles.

It would have been obvious to use VEGF 121 as a targeting ligand because it is an art recognized variant of VEGF. See Tischer above. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case the essential function and intended use of VEGF/VEGF 121 is to recognize and bind to the receptor.

Thus the invention as a whole was *prima facie* obvious.

Claims 1-3, 5-9, 13-17, 19-23, 27-33, 35-39, and 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bally et al (US Patent 4,885, 172, issued 12/5/1989) in view of Valerio et al (WO 97/05266, published 2/13/97), and Skerra et al (US Patent 5,506,121, issued 4/9/96).

Bally teaches a composition and methods for delivering bioactive materials comprising a liposomal carrier, wherein the lipids are covalently modified with the adapter streptavidin, and biotinylated targeting antibodies are then bound to the adapter. See abstract. In one embodiment, the bioactive material is the chemotherapeutic reagent doxorubicin. See column 3, lines 36-41. In another

embodiment the bioactive material is a polynucleotide. See column 6, lines 24 and 25. The antibodies recognize cell surface antigens. See e.g. column 4, lines 15-17. The compositions are delivered in an aqueous solution, as required by instant claim 45. See column 9, lines 51-54.

Bally does not teach a targeting antibody that comprises a peptide that recognizes streptavidin.

Valerio teaches a method of producing viral gene delivery vehicles which can be transferred to pre-selected cell types by using targeting conjugates. The gene delivery vehicles comprise a carrier with a member of a specific binding pair (adapter), the counterpart of which is not directly associated with the surface of the target cell. The targeting conjugates are composed of the counterpart member of the specific binding pair linked to a targeting moiety which is a cell-type specific ligand. The member of the specific binding pair present on the vehicle can be streptavidin. See abstract and column 8, lines 15-35. The targeting conjugate may be a fusion protein. See page 9, lines 14-23. See also page 16, lines 8-27. This passage also discusses the use of spacers for separating the targeting moiety and the binding pair member. Valerio teaches that the targeting moiety may be an antibody. See page 13, lines 21-32, and page 16, lines 16-32

Skerra teaches methods and constructs for making fusions to peptides with binding affinity for streptavidin. See abstract.

It would have been obvious to one of ordinary skill in the art to use the fusion constructs of Skerra in making a fusion targeting protein as taught by Valerio, e.g. a

streptavidin binding peptide/targeting antibody fusion. One would have been motivated to do so because Valerio explicitly teaches that streptavidin may be used as a binding partner attached to a carrier vehicle, that targeting conjugates comprising a binding partner for streptavidin may be used, that targeting moieties may be antibodies, and that targeting conjugates may be fusion proteins. Further, the fusion protein of Skerra can be produced in large quantities by recombinant methods, and easily purified on a streptavidin affinity column. In contrast, other recombinantly produced targeting ligands would have to be biotinylated prior to use in the system of Valerio, thereby requiring further preparation steps, more time, and possible loss of material.

It would have been similarly obvious to use the recombinant fusion targeting protein described above to target the liposomes of Bally. One would have been motivated to do so because the fusion polypeptide is easily produced by recombinant means, easily purified, and requires no further biotinylation step, as discussed above.

Claims 5, 19, and 35 are included in the rejection because the lipids comprise polymers of methylene groups in their hydrophobic tails, and because the carried nucleic acid can also be considered to be a polymer comprised by the carrier.

Claims 13, 27, and 43 are included in this rejection because Bally teaches the use of antibodies to target liposomes to the class I MHC antigen, H-2. See column 2, lines 15-18. Class I MHC molecules such as H-2 are present on all nucleated cells including vascular endothelial cells.

It is noted that Bally does not explicitly teach the organization of the elements of the composition into a kit with instructions for use. However, it would have been

obvious to organize these materials into a kit with instructions for use because one of skill in the art appreciates that organizing experimental reagents prior to use and following established protocols is standard laboratory practice which reduces the frequency of errors.

Claims 10, 24, 40, 58-64, 66-74, and 76-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bally et al (US Patent 4,885, 172, issued 12/5/1989), Valerio et al (WO 97/05266, published 2/13/97), and Skerra as applied to claims 1-3, 5-9, 13-17, 19-23, 27-33, 35-39, and 43-45 above, and further in view of Allen et al (US 2001/0038851, published 11/8/01), and Tischer et al (US 5,194,596, issued 3/16/93).

The teachings of Bally, Valerio, and Skerra are summarized above and can be combined to render obvious a composition comprising a streptavidin conjugated liposomal carrier and a recombinant fusion targeting protein comprising a streptavidin-binding moiety and a targeting moiety.

These references do not teach the use of VEGF 121 as a targeting moiety.

Allen teaches that VEGF can be used as a targeting moiety in delivery complexes.

Tischer teaches that VEGF 121 is an art recognized equivalent of VEGF in terms of its function in wound healing. See column 3, line 67 to column 4, line 9, Fig, 7, and column 10, lines 63-68. Clearly this function entails binding its receptor.

It would have been obvious to one of ordinary skill in the art at the time of the invention to use VEGF 121 as a targeting moiety in a fusion targeting construct of

Valerio. One would have been motivated to do so because Valerio teaches that ligands that recognize cellular receptors should be used as targeting moieties, and because Allen teaches that VEGF is a useful targeting ligand in the context of delivery vehicles. It would have been obvious to use VEGF 121 as a targeting ligand because it is an art recognized variant of VEGF. See Tischer above. MPEP 2144.06 indicates that when it is recognized in the art that elements of an invention can be substituted, one for the other, while retaining essential function, such elements are art-recognized equivalents. An express suggestion to substitute one equivalent component or process for another is not necessary to render such substitution obvious. In re Fout, 675 F.2d 297, 213 USPQ 532 (CCPA 1982). Furthermore, MPEP 2144.07 indicates that the selection of a known material based on its suitability for its intended use supports the determination of prima facie obviousness. See also Sinclair & Carroll Co. v. Interchemical Corp., 325 U.S. 327, 65 USPQ 297 (1945). In this case the essential function and intended use of VEGF/VEGF 121 is to recognize and bind to the receptor.

It would have been similarly obvious to use the recombinant fusion targeting protein described above to target the liposomes of Bally. One would have been motivated to do so because the fusion polypeptide is easily produced by recombinant means, easily purified, and requires no further biotinylation step, as discussed above.

Thus the invention as a whole was *prima facie* obvious.

Claims 11, 25, 41, 65, and 75 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bally et al (US Patent 4,885, 172, issued 12/5/1989), Valerio et al

(WO 97/05266, published 2/13/97), and Skerra as applied to claims 1-3, 5-9, 13-17, 19-23, 27-33, 35-39, and 43-45 above, and further in view of Theodore et al (US Patent 6,075,010, issued 6/13/00).

The teachings of Bally, Valerio, and Skerra are summarized above and can be combined to render obvious a composition comprising a streptavidin conjugated liposomal carrier and a recombinant fusion targeting protein comprising a streptavidin-binding moiety and a targeting moiety.

These references do not teach the use of S protein and S-peptide as a binding pair or, more specifically, the use of S protein as an adapter and the use of S-peptide as a recognition moiety in a targeting fusion protein.

It would have been obvious to one of ordinary skill in the art at the time of the invention to modify the teachings of Bally, Valerio, and Skerra by using the S-protein and S-peptide binding pair of Theodore. One would have been motivated to do so because Theodore indicates that this binding pair is equivalent to other binding pairs such as the biotin streptavidin binding pair taught by Valerio.

Thus the invention as a whole was *prima facie* obvious.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441. The examiner can normally be reached Monday through Friday between the

hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, can be reached at 703-306-3217. The official central fax number is 703-872-9306. Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

DAVE T. NGUYEN
PRIMARY EXAMINER

Richard Schnizer, Ph.D.